Docket No.: PF-0532-2 DIV

Response Under 37 C.F.R. 1.116 - Expedited Procedure
Examining Group 1644

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By: Diane Kizer Printed: Diane Kizer

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Application of: Hillman et al.

Title:	DELTA-1-PYRROLINE-5-CARBOXYLATE REDUCTASE HOMOLOG		
Serial No.:	09/912,717	Filing Date:	July 24, 2001
Examiner:	Huynh, P.	Group Art Unit:	1644

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REPLY BRIEF

Sir:

This is Appellants' Reply Brief On Appeal (submitted in triplicate) in response to the Examiner's Answer dated 06/12/03 ("the Examiner's Answer") in the above-identified application (the Hillman '717 application).

In the Examiner's Answer the Patent Examiner:

(1) maintained the rejection of Claims 45, 47, 49-50, 52, 60 and 61 under 35 U.S.C. § 112, first paragraph for alleged lack of enablement,;

(2) maintained the rejection of Claims 45, 47, 49-50, 52, 60 and 61 under 35 U.S.C. § 112, first paragraph for alleged lack of written description of the claimed polynucleotide variants;

(3) withdrew the rejection of Claims 46 and 54-59 under 35 U.S.C. § 112, first paragraph for alleged lack of enablement.

(4) withdrew the rejection of Claims 46 and 54-59 under 35 U.S.C. § 112, first paragraph for alleged lack of written description.

I. Rejections for lack of enablement under 35 U.S.C. § 112, first paragraph.

The Examiner has maintained the rejection of Claims 45, 47, 49-50, 52, 60 and 61 under 35 U.S.C. § 112, first paragraph for alleged lack of enablement. In maintaining the rejection, the Examiner concedes that the issue is not making the antibody, but rather the binding specificity of the antibody (See 6/12/03 Examiner's Answer, at page 11). The crux of the Examiner's argument is based on the repeated contention that "Immunization with a single peptide fragment derived from a full-length polypeptide **may** result in antibody specificity that differs from the antibody specificity directed against the full-length polypeptide (06/12/03, Examiner's Answer, at pages 9, 11 and 12). The Examiner attempts to support the above position by citing Kuby et al. (Kuby et al: Immunology, Second edition, W.H. Freeman and Company, New York, NY, page 94, 1994.)

The Examiner's argument is both without merit and contrary to the law. First, there is simply no requirement, legal or otherwise, that the claimed antibodies have the same specificity as the antibody that binds to the full length polypeptide comprising SEQ ID NO:1. Further, nowhere does the Specification require that a particular antibody that specifically binds a protein having the sequence of SEQ ID NO:1 also bind every conceivable variant thereof with exactly the same affinity. The antigen that may be used to induce the claimed antibodies is not restricted to a polypeptide having the amino acid sequence of SEQ ID NO:1.

Also, even if there were such a requirement, which there is not, the Examiner provides no evidence, let alone proof, for differing antibody specificity resulting from a single amino acid substitution of the claimed antibodies. Having failed to do so, the Examiner's contention lacks proper evidentiary relevance as established by case law. As the court stated in *Boehringer Ingelheim Vetmedica Inc. v. Schering-plough Corporation*, the "fact that even a single nucleotide or amino acid substitution may drastically alter the function of a gene or protein is not evidence of anything at all." *Boehringer Ingelheim Vetmedica Inc. v. Schering-Plough Corp.*, 320 F.3d 1339,1351 (Fed. Cir. 2003). Like *Boehringer*, the Examiner's conjecture that an amino

acid substitution may affect antibody specificity is not "not evidence of anything at all." Because the rejection is predicated on a contention that is without merit, lacks evidentiary relevance and is in contradiction to case law, it should be reversed.

The Examiner also maintains the rejection on several other assertions that are erroneous in nature. First, the Examiner contends that the Specification provides "no guidance as to which primers and PCR condition (sic) to obtain 'naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:1." (06/12/03 Examiner's Answer, at page 10). This contention is in error. The Specification provides extensive teaching on both PRC conditions and primers. Such teaching includes, but is not limited to, the following:

> As used herein, the term "stringent conditions" refers to conditions which permit hybridization between polynucleotides and the claimed polynucleotides. Stringent conditions can be defined by salt concentration, the concentration of organic solvent, e.g., formamide, temperature, and other conditions well known in the art. In particular, stringency can be increased by reducing the concentration of salt, increasing the concentration of formamide, or raising the hybridization temperature. (Specification at page 11, lines 2-6)

> For all PCR-based methods, primers may be designed using commercially available software, such as OLIGO™ 4.06 Primer Analysis software (National Biosciences Inc., Plymouth, MN) or another appropriate program, to be about 22 to 30 nucleotides in length, to have a GC content of about 50% or more, and to anneal to the template at temperatures of about 68°C to 72°C. (Specification at page 15, lines 20-24).

> In one aspect, hybridization with PCR probes which are capable of detecting polynucleotide sequences, including genomic sequences, encoding P5CRH or closely related molecules may be used to identify nucleic acid sequences which encode P5CRH. The specificity of the probe, whether it is made from a highly specific region, e.g., the 5' regulatory region, or from a less specific region, e.g., a conserved motif, and the stringency of the hybridization or amplification (maximal, high, intermediate, or low), will determine whether the probe identifies only naturally occurring sequences encoding P5CRH, allelic variants, or related sequences.Probes may also be used for the detection of related sequences, and should preferably have at least 50% sequence identity to any of the P5CRH encoding sequences.

> The hybridization probes of the subject invention may be DNA or RNA and may be derived from the sequence of SEQ ID NO:2 or from genomic sequences including promoters, enhancers, and introns of the P5CRH gene.(Specification at page 31, lines 3-13).

The Examiner's attention is also directed to Example V at pages 39-40 of the Specification for further teaching on PCR conditions and primers.

The Examiner also now argues that "the use of 'percent' in conjunction with any of the various terms that refer to sequence similarity is a problem since sequence identity between two sequences has no common meaning within the art" and that gap scoring "introduces uncertainty as to the percent of similarity between two sequence." (6/12/03 Examiner's Answer, at page 10) This contention is untenable. First "percent identity" is explicitly defined in the Specification at page 8, lines 31-32. Further, the methodology for calculating sequence similarity, which includes accounting for gaps, is specifically described in the Specification at page 9, lines 1-5.

The Examiner continues with the above line of argument by with the contention that "the problem of predicting functional aspects of the product from mere sequence data of a single nucleic acid sequence and what changes can be tolerated is complex and well outside the realm of routine experimentation."(6/12/03 Examiner's Answer, at page 10). This contention, presented without scientific authority or any scientific reasoning, sound or otherwise, is untenable. It is also in direct contradiction to the scientific reference, Brenner, et al, presented by Appellants in their Appeal Brief. (See 3/23/03 Appeal Brief, at page 14).

Finally, the Examiner maintains the rejection on the contention that "[t]he specification does not teach any other polypeptide such as variants to the amino acid sequence of SEQ ID NO:1 that has 90% identity to SEQ ID NO:1 having 1-pyrroline-5-carboxylate reductase activity." (6/12/03 Examiner's Answer, at page 9). This argument, which is essentially a restatement of the Examiner's arguments in the Final Office Actions (see 9/30/02 Final Office Action, at page 6) is without merit because the Specification specifically describes variants to the amino acid sequence of SEQ ID NO:1, including variants at least 90% identical to the amino acid sequence of SEQ ID NO:1 having 1-pyrroline-5-carboxylate reductase activity (see the Specification at page 2, lines 30-36, page 5, lines 21-24; and page 12, lines 33-36). The Examiner's Answer fails to respond to or even consider this point which was described in the 3/23/03 Appeal Brief (See 3/23/03 Appeal Brief at page 4).

Further, by continuing to maintain the rejection based on the above contention without providing objective reasons for the rejection, the Examiner's Answer is in contradiction to the holding set forth in *In re Marzocchi.* 169 U.S.P.Q. 367, 369 (CCPA 1971):

> The first paragraph of § 112 requires nothing more than objective enablement. How such a teaching is set forth, either by the use of illustrative examples or by broad terminology, is of no importance.
>
> As a matter of Patent Office practice, then, a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented *must* be taken as in compliance with the enabling requirement of the first paragraph of § 112 *unless* there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.

Contrary to the standard set forth in *In re Marzocchi*, the Examiner has failed to provide any ***reasons*** why one would doubt that the guidance provided by the present Specification would enable one to make and use the recited antibodies to SEQ ID NO:1 or to its variants. Hence, a *prima facie* case for non-enablement has not been established with respect to the recited variants of SEQ ID NO:1.

For all the reasons above, Appellants request reversal of the enablement rejection.

II. Rejections for lack of written description under 35 U.S.C. § 112, first paragraph.

The Examiner has maintained the rejection of Claims 45, 47, 49-50, 52, 60 and 61 under 35 U.S.C. § 112, first paragraph for alleged lack of written description. The Examiner's Answer maintains this rejection based on the contention that there is inadequate written description of "any naturally-occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:1." (6/12/03 Examiner's Answer, at page 15).

This rejection, is improper, as the claims define subject matter which is described in the Specification in such a way as to reasonably convey to one skilled in the art that the inventors had possession of the claimed subject matter at the time the application was filed.

First note that the "variant" language of independent claim 45 recites polypeptides "comprising a naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:1, said naturally occurring amino acid sequence having 1-pyrroline-5-carboxylate reductase activity." The polypeptide sequence of SEQ ID NO:1 is explicitly disclosed in the Specification (see, e.g. the Sequence Listing and Figures 1A, 1B, 1C, 1D and 2

of the Specification). Variants of SEQ ID NO:1 are described in the Specification at, for example, page 2, lines 30-36; page 5, lines 21-24; and page 12 lines 33-39. In addition, a specific assay to measure P5CRH activity is disclosed in the Specification at, for example, page 43, line 7 to page 44 line 10. The Specification also describes the production of antibodies to P5CRH proteins at, for example, page 6, lines 32 to page 7, line 1.

Appellants submit that one of ordinary skill in the art would recognize polypeptide sequences which are variants that are at least 90% identical to SEQ ID NO:1. Given any naturally occurring polypeptide sequence, it would be routine for one of skill in the art to recognize whether it was a variant of SEQ ID NO:1. It would also be routine to determine whether such a variant had P5CRH activity, using the disclosed P5CRH assay. Accordingly, the Specification provides an adequate written description of the claimed antibodies which specifically bind to the recited polypeptide variants of SEQ ID NO:1.

The Examiner maintains the written description rejection on the contention that "there is inadequate written description about the binding specificity, the antigenic determinant of the claimed antibody and the epitope to which the claimed antibody binds" (See 06/12/03 Examiner's Answer, at page 15). This argument is irrelevant since the claims do not recite antibody binding specificity, antigenic determinant or an epitope. While such information might be useful in some circumstances, there is simply no legal requirement that the specification or claims provide such information in order to meet the written description provisions of 35 U.S.C. § 112, first paragraph.

For all the reasons above, Appellants request reversal of the written description rejection.

III. CONCLUSION

For all the foregoing reasons and the reasons stated in Appellants' Brief on Appeal, it is submitted that the Examiner's rejections of the claims on appeal should be reversed.

If the USPTO determines that any additional fees are due, the Commissioner is hereby authorized to charge Deposit Account No. **09-0108.**

This brief is enclosed in triplicate.

Respectfully submitted,

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